

EDITORIAL COMMENT

Plaque Rupture and Intracoronary Thrombus in Nonculprit Vessels

An Eyewitness Account*

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Over the last 25 years, there has been enormous progress in understanding the pathogenesis of acute coronary syndromes (ACS) and the pathobiology of atherosclerosis and atherothrombosis. Nonocclusive, mural, or occlusive intracoronary thrombus (ICT) has been established as the cause of nearly all acute myocardial infarctions (AMIs), a majority of non-ST-segment elevation ACS, and a large proportion of patients with sudden cardiac death (SCD) (1,2). The atherosclerotic process underlying ICT is usually either plaque disruption (PD) or erosion (3). Plaque inflammation “fuels the fires” of atherosclerosis contributing to plaque disruption and erosion, as well as to the initiation and progression of the atherosclerotic process (4).

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In addition to its important role in ACS, incorporation of thrombus into the vessel wall has been found to be a mechanism for the asymptomatic progression of atherosclerosis (5). The thrombus organizes and becomes covered by neointima, increasing plaque burden and contributing to a reduction in lumen diameter. Along with plaque hemorrhage, presumably from rupture or leakage of vasa vasorum that has neovascularized the plaque (6), these two processes contribute significantly to the non-linear progression of atherosclerosis.

Recent information has also indicated that PD and/or ICT may be multifocal and not limited to the culprit lesion in patients presenting with an ACS. Multiple studies utilizing different imaging modalities for analysis have confirmed or expanded upon previous pathologic studies of the coronary arteries from patients dying of AMI or SCD, showing that multiple sites of “vulnerable plaque” or PD may be present in a significant percentage of patients (7–11). Most of these other sites are clinically silent, and multiple PDs may be accompanied by a heightened systemic inflammatory response (12,13).

Despite the recent progress made in elucidating the role of ICT in ACS and the progression of atherosclerosis, the

imaging modalities in humans have significant limitations in defining ICT. Although coronary angiography is used extensively for this purpose, it is not a sensitive modality for thrombus detection or in following the asymptomatic progression of atherosclerosis. Intravascular ultrasound can quantitatively analyze changes in atherosclerotic progression but cannot adequately differentiate soft plaque from thrombus (14). Although it is not widely available, angioscopy is currently the only in vivo technique to accurately assess the presence of ICT in coronary artery disease, since it directly visualizes the luminal surface of the vessel wall. Although greatly limited by patient selection and technical challenges (i.e., balloon occlusion of the coronary artery before visualization), angioscopy has provided insight into the pathophysiology of ACSs, the natural history of thrombus after myocardial infarction, and the mechanism of acute closure after balloon angioplasty (15–17).

In this issue of the *Journal*, Takano et al. (18) utilized angioscopy to evaluate by direct visualization 48 thrombi in 50 ruptured coronary plaques from non-culprit lesions in 30 patients. Percent diameter stenosis of the target plaques by quantitative coronary angiography analysis and the serum C-reactive protein (CRP) level were measured (18). The mean angioscopic follow-up period was 13 ± 9 months. Superimposed thrombi still remained at follow-up in 35 lesions, and the predominant thrombus color changed from red (56%) at baseline to pinkish-white (83%) at follow-up. The healing rate of ICT increased according to the angioscopic follow-up period (<12 months, 23% vs. >12 months, 55%; $p = 0.044$). The percent diameter stenosis at the healed plaque increased from baseline to follow-up ($12.3 \pm 5.8\%$ vs. $22.7 \pm 11.6\%$), whereas in non-healed plaque, there was no angiographic progression. The serum CRP level in patients with healed plaques ($n = 10$) was lower than in those without healed plaques ($n = 19$), (0.07 ± 0.03 mg/dl vs. 0.15 ± 0.11 mg/dl, respectively; $p = 0.007$), and statin use was significantly more common in patients with healed plaque. The authors concluded that ruptured plaques in nonculprit lesions tended to heal slowly with a progression of angiographic stenosis, and the serum CRP level might reflect the disease activity of ruptured plaques.

The findings of Takano et al. (18) provide several interesting observations. Intracoronary thrombus was present in nonstenotic lesions and associated in $>90\%$ of cases with underlying plaque rupture. Intracoronary thrombus persisted over time, and healed thrombus contributed to the asymptomatic progression of angiographic stenosis. Higher CRP and no statin use predicted the non-healing (persistence of thrombus) in univariate analysis, although not in their multivariate analysis. Previous work has suggested that elevated CRP may predict progression of atherosclerosis in this population (19). That ICT would persist over time suggests that there is a persistent inflammatory or thrombotic stimulus. Although it was possible that the ICT visualized represented recurrent thrombus and not persis-

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tent thrombus, the exact mechanism for this persistent thrombus remains elusive. Given the known interrelationship between inflammation and thrombosis, a heightened inflammatory state could promote a prothrombotic milieu (20).

Another interesting and unexplained observation was related to thrombus color as detected by angiography. In an ACS without total occlusion, the thrombus is usually white and presumed platelet-rich. Only with total occlusion was the thrombus red, with red cells and fibrin overlying a nidus of platelets (15). In the Takano et al. study (18), the nonocclusive thrombus in nonobstructed arteries was red in a majority of cases. On the other hand, a white thrombus as seen in unstable angina requires significant luminal obstruction at the site of PD and altered flow patterns (high shear rates) in addition to a prothrombotic milieu (21). Although pinkish-white thrombus was detected by Takano et al. (18) on follow-up, we suspect that this represents a partially healed thrombus, with the white color related to collagen admixed with thrombotic components.

Lastly, as discussed in this paper, what determines if the thrombus is asymptomatic or leads to clinical manifestations? As pointed out by Takano et al. (18), the presence of symptoms is multifactorial and dependent on several factors, including atherosclerotic plaque burden, percent diameter narrowing, and the prothrombotic milieu.

This article, although thought-provoking, has several limitations. 1) The patient population was small and highly selected. 2) It remains unknown what method was used to measure CRP and what the upper limits of normal were. 3) There was also no measurement of additional thrombotic markers such as fibrinogen, and the duration of antithrombotic therapy in patients with or without healing ICT was unknown. 4) Whether there was progression of angiographic diameter stenosis at follow-up in lesions without thrombosis (a control group) was not reported. 5) The original percutaneous coronary intervention may have contributed to nonhealing of ICT (injury from the wire or balloon) if the nonculprit ICT was in the same vessel as the original intervention.

Despite the above limitations, the paper by Takano et al. (18) contributes to our understanding of ICT as observed in vivo, including its role in the asymptomatic progression of atherosclerosis. In the future, improvements in non-invasive and invasive imaging may expand on these observations in a larger and less selected population. These data also suggest a potential role for appropriate long-term antithrombotic/anticoagulant therapy, not only in reducing future acute coronary events but also as anti-atherosclerotic therapy.

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